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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/133,914	08/13/98	PORTNOY	B98-029

RICHARD ARON OSMAN
SCIENCE AND TECHNOLOGY LAW GROUP
75 DENISE DRIVE
HILLSBOROUGH CA 94010

HM12/0721

EXAMINER	
RAILEY, J	
ART UNIT	PAPER NUMBER
1636	3

DATE MAILED:

07/21/99

Please find below a communication from the EXAMINER in charge of this application

Commissioner of Patents

Office Action Summary

Application No.

09/133,914

Applicant(s)

Portnoy et al.

Examiner

J. Railey

Group Art Unit

1636



☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-10 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-3 and 6-9 is/are rejected.

☒ Claim(s) 4, 5, and 10 is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

The drawings submitted 13 August 1998 have been approved by the draftsman.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Darji et al. [Cell 91:765-775 (1997)].

Darji et al. teach attenuated strains of *S. typhimurium* which have been transformed with

eukaryotic expression vectors comprising the *Listeria monocytogenes* virulence factors, truncated forms of listeriolysin and ActA. These virulence factors are expressed from the control of a eukaryotic promoter and therefore are not expressed by the host bacterium. The reference shows at Figure 8 that the attenuated, transformed bacteria are endocytosed up by individual phagocytic cells and are subsequently lysed within the individual cells, releasing their contents within the eukaryotic cells.

Applicant claims nonvirulent bacterium comprising a first gene encoding a nonsecreted foreign cytolysin operably linked to a heterologous promoter and a second gene encoding a different foreign agent. Also claimed are embodiments in which the cytolysin is absent a functional signal sequence or is listeriolysin. The bacterium may encode a foreign agent "therapeutic to a eukaryote." (As defined in the specification at page 4, this may include immunogens.) Eukaryotic cells or phagocytic cells comprising the nonvirulent bacteria are also claimed. A method of introducing a foreign agent into a eukaryotic cell is claimed in which the transformed bacterium is contacted with the eukaryotic cell under conditions whereby the agent "enters the cell." The difference between what is *claimed* by applicant and the prior art is that the prior art describes the *S. typhimurium* as "attenuated" while applicant calls their bacterium "nonvirulent." The terms are essentially interchangeable in that the transformed bacteria of the prior art do not cause active disease within the host to which they are administered.

In order to obviate this ground of rejection, applicant is encouraged to review the

specification as filed and amend the claims such that the nature of the expression of the genes introduced into the nonvirulent bacterium are more clearly claimed. For instance, it is evident that applicant's invention is that the non-secreted cytolysin, and a gene of interest, are both expressed by prokaryotic promoters such that the cytolysin and the protein of interest ("foreign agent") remain within the nonvirulent bacterial cell. When the bacterial cell is endocytosed by a phagocytic eukaryotic host cell, the bacterial cell is degraded within the phagosome and the released cytolysin functions to lyse the phagosomal membrane within the eukaryotic cell and thereby facilitate the delivery of the protein of interest ("foreign agent") to the host eukaryotic cell. The critical element of applicant's invention is that the cytolysin is already expressed and present within the transformed bacterial host prior to that cell's contact with the eukaryotic cell.

It is evident that the claimed "agent" may be either protein or nucleic acid. See applicant's work by Higgins et al. [Molecular Microbiology **31(6)**:1631-1641 (1999)] and the review of bacterial delivery systems in Higgins et al. [Nature Biotechnology **16(2)**:138-139 (1998)]. Applicant's work is different from that taught by Ikonomidis et al. [Journal of Experimental Medicine **180(6)**:2209-2218 (1994)] in that Ikonomidis et al. teach not only the use of a pathogenic host cell, *Listeria monocytogenes*, but also that the listeriolysin is secreted as a fusion protein. Applicant's work also differs from any of the patents to Curtis, III or Curtis III, et al. [U.S. Patents 4,888,170; 5,294,441; 5,387,744; 5,424,065; 5,855,879 and 5,855,880] because although these patents teach avirulent bacteria for delivery of a "foreign agent" (protein), they do not teach

the use of a cytolysin operably linked to a heterologous promoter as part of the host bacterial delivery vehicle. Further, the patents to Branstrom et al. [U.S. patent 5,824,538] and Powell et al. [U. S. Patent 5,877,159] teach expressly that the purpose of the bacterial delivery systems are to deliver nucleic acid which is subsequently expressed by the eukaryotic host cell, and do not teach the expression of a cytolysin within the bacterial host cell by means of a heterologous promoter.

Claims 4 and 5 are free of the prior art because the prior art does not teach bacteria comprising the genes as claimed

Claim 10 is free of the prior art because of the limitation that the cytolysin mediates the transfer of the agent from the vacuole to the cytosol of the cell. The prior art of Darji et al. does not teach or suggest that the listeriolysin has been expressed and is present within the host bacterial cell.

Claims 4, 5 and 10 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Art Unit 1636 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number for Art Unit 1636 is (703) 308-4242 or 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner

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Art Unit: 1636

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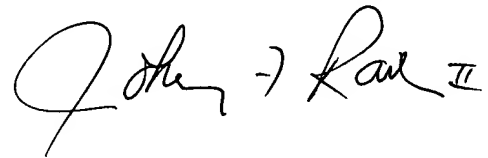
should be directed to J. F. Railey, whose telephone number is (703) 308-0281. The examiner can normally be reached on Monday-Thursday, and alternate Fridays, from 8:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax phone number for informal transmissions to the examiner is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

19 July 1999

JOHNNY F. RAILEY II, PH.D.
PRIMARY EXAMINER
TECHNOLOGY CENTER 1600

A handwritten signature in black ink, appearing to read "Johnny F. Railey II". The signature is written in a cursive, flowing style with a large initial "J" and a distinct "II" at the end.